REMARKS

The Examiner rejected claims 1, 6-11, 23, and 25. Applicant has amended claim 1 to remove the phrase "in response to a vasoconstrictor agonist." Applicant also has amended claim 25 to remove the terms "KCl" and "serotonin." In addition, Applicant has amended claims 1 and 25 to recite a method to normalize the contractile response of vasculature having a vascular smooth muscle cell layer and a compromised endothelial cell layer. Support for this amendment can be found in Applicant's specification at, for example, page 15, line 8 and in Figure 1, which teach that normal vasculature (blood vessels) include a smooth muscle cell layer and an endothelial cell layer. Applicant's specification also teaches that vascular smooth muscle (VSM) is covered by an endothelial layer of cells that can modulate the activation of chloride ion channels in the VSM by vasoconstrictor agonists such as norepinephrine. See, for example, page 1, line 8 to page 2, line 22. Thus, no new matter has been added.

In light of these amendments and the following remarks, Applicant respectfully requests reconsideration and allowance of claims 1, 6-11, 23, and 25.

Interview summary

Applicant's agents thank Examiner Kim for the courtesy of a telephonic interview on July 12, 2004. During the interview, the outstanding rejections and proposed responses were discussed. While no agreements were definitively reached, the interview resulted in a greater understanding of the Examiner's rejections.

Initialed PTO Forms 1449

Supplemental Information Disclosure Statements and PTO Forms 1449 were submitted to the United States Patent & Trademark Office on March 22, 2002 and November 13, 2003. To date, however, initialed copies of these forms have not been returned to Applicant's agents. Applicant respectfully requests that the Examiner review the cited documents and return copies of the initialed forms to the undersigned representative.

Rejections under 35 U.S.C. § 112

The Examiner rejected claim 25 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner stated that the term "serotonin" lacks literal support in the specification, and thus is subject to a new matter rejection.

Applicant has removed the term "serotonin" from claim 25. As such, the Examiner's rejection is moot.

The Examiner also rejected claims 1, 6-11, and 23 under 35 U.S.C. § 112, first paragraph, for lack of enablement. Specifically, the Examiner stated that the specification does not reasonably provide enablement for the term "a vasoconstrictor agonist," and that a person of ordinary skill in the art is not enabled to practice the invention commensurate in scope with the claims.

Applicant respectfully disagrees. To further prosecution, however, Applicant has amended claim 1 to remove the phrase "in response to a vasoconstrictor agonist." In light of this amendment, Applicant respectfully requests withdrawal of the rejection of claims 1, 6-11, and 23 under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 103

The Examiner maintained the rejection of claims 1, 6-11, and 23 under 35 U.S.C. § 103(a) as being unpatentable over the Grainger *et al.* patent (U.S. Patent No. 6,197,789) for the reasons stated in the previous Office Action. In the previous action, the Examiner stated that the Grainger *et al.* patent teaches that Applicant's active agent is useful to inhibit the pathological activity of vascular smooth muscle cells (VSMC) by inhibiting activation, including contraction. The Examiner also asserted that the disclosure of "inhibiting contraction" encompasses "normalization," since the "inhibition of contraction" would have the same effect as "normalization." Thus, the Examiner concluded that the Grainger *et al.* patent renders the present claims obvious.

Applicant respectfully disagrees. A person of ordinary skill in the art reading the Grainger *et al.* patent would not have been motivated to normalize vasoconstriction of

vasculature having a compromised endothelial layer by administering an agent such as tamoxifen. This is particularly true given that the Grainger *et al.* patent fails to provide any evidence that tamoxifen can affect vasoconstriction. In contrast, the Grainger *et al.* patent discloses experimental data showing that tamoxifen treatment of VSMC in culture can decrease cell proliferation and increase levels of TGF-beta, while tamoxifen treatment of mice on a high fat diet can reduce the formation of aortic lipid lesions.

At no point does the Grainger *et al.* patent provide any evidence to indicate that tamoxifen has an effect on contractile VSMC (i.e., mature, non-proliferative VSMC). A person of ordinary skill in the art would appreciate that contractile and proliferative VSMC serve different purposes, and thus have widely different properties. See, for example, Owens (1995) *Physiol. Rev.* 75:487-517 (copy enclosed). This review teaches that mature VSMC proliferate at an extremely low rate and are almost completely geared for contraction, expressing a unique repertoire of contractile proteins, ion channels, and signaling molecules that clearly distinguish mature VSMC from any other cell type. In contrast, the principal function of VSMC during vasculogenesis is proliferation and production of matrix components of the blood vessel wall. Thus, the Owens review teaches that proliferative and contractile VSMC are two very different cell types that express different groups of genes. The Grainger *et al.* patent discloses only that tamoxifen has an effect on proliferative VSMC. Since the Grainger *et al.* patent fails to provide support for the notion that tamoxifen would affect the contractile activity of mature VSMC, a person having ordinary skill in the art reading this reference would not have been motivated to use tamoxifen to normalize vasoconstriction of endothelially-compromised VMSC, because there would have been no reasonable expectation of success.

Moreover, Applicant's specification teaches that the effect of tamoxifen on VSM was not firmly established even after the Grainger *et al.* patent was filed. See, for example, the sections of Applicant's specification at page 2, lines 12-15 and extending from page 26, line 21 to page 27, line 11. These sections disclose that at the time the present application was filed, the inventor believed that norepinephrine-induced contraction of normal vasculature (i.e., vasculature having an intact endothelium) was not affected by tamoxifen treatment. These sections further disclose that due to the lack of effect on normal VSM, the inventor did not

previously examine the effect of tamoxifen on endothelially-compromised VSM. In addition, these sections of the specification also disclose that Applicant's previous findings were published as Lamb and Barna (1998) *Am. J. Physiol.* 275:H151-H160, and Lamb and Barna (1998) *Am. J. Physiol.* 275:H161-H168 (both listed on the Form 1449 mailed to the Patent and Trademark Office on June 18, 2001). Thus, as of 1998, the effect of tamoxifen on normal VSM was uncertain. Due to this uncertainty, a person of ordinary skill reading the Grainger *et al.* patent would not have had a reasonable expectation that tamoxifen would affect VSM associated with vasculature having a compromised endothelial layer.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 1, 6-11, and 23 under 35 U.S.C. § 103(a).

Rejection under 35 U.S.C. § 102

The Examiner rejected claim 25 under 35 U.S.C. § 102(b) as being anticipated by the Stromberg patent (U.S. Patent No. 5,470,883) evidence by the Kifor *et al.* patent (U.S. Patent No. 5,658,936). In particular, the Examiner stated that it is inherent that administration of tamoxifen to patients treated with norepinephrine, as disclosed by the Stromberg patent, "would normalize (reverse, inhibit) the contractile response of endothelially-compromised vascular smooth muscle."

Applicant respectfully disagrees. In order to anticipate a claim, a reference must teach every element of that claim. MPEP § 2131. The Stromberg patent fails to disclose that tamoxifen can be used to normalize contraction of vasculature having a VSMC layer and a compromised endothelial layer. Rather, the Stromberg patent discloses that administration of tamoxifen to normal rabbits can reduce the level of vasoconstriction induced by epinephrine. At no point, however, does the Stromberg patent disclose that tamoxifen has any effect on vascular smooth muscle with an endothelial layer that is compromised or damaged by disease, mechanical manipulation, or any other means. Thus, this reference does not teach all elements of claim 25.

During the telephonic interview, the Examiner indicated that injection of epinephrine into the ear arteries of rabbits, as disclosed in the Examples of the Stromberg patent, would result in endothelial compromisation. Applicant respectfully asserts that the Examiner's statement is

incorrect. Applicant's specification teaches that vasculature includes a layer of VSMC in contact with a layer of endothelial cells that can modulate vasoconstrictor-induced contraction of the VSMC. See, for example, page 1, line 8 to page 2, line 22, page 15, line 8, and Figure 1. Applicant's specification also teaches that disruption of the endothelial layer increases the sensitivity of the VSMC to vasoconstrictor agonists. Vasoconstrictor agonists themselves, however, are not considered to cause endothelial compromisation of VSM. Rather, Applicant's specification at page 3, lines 10-19, for example, teaches that endothelial damage can result from medical procedures and/or pathologies such as diabetes or hypertension, which may be exacerbated by endothelial damage.

Applicant further submits that the separation between endothelial compromisation and treatment with vasoconstrictor agonists is supported by Lamb and Barna publication (1998) *Am. J. Physiol.* 275:H151-H160. In this publication, the inventor disclosed that tamoxifen had no significant effect on the contractile response of intact VSM in rat aortic rings treated with norepinephrine or KCl. See, the right column on page H155 of the Lamb and Barna publication. In contrast, the Examples and Figures 2 and 3 of the present application disclose that tamoxifen did reduce the contractile response of denuded VSM in rat aortic rings. Moreover, the Examples and Figures 2 and 3 indicate that tamoxifen did not affect the response of intact VSM to either norepinephrine or KCl. Thus, treatment with a vasoconstrictor agonist alone does not cause VSM to become endothelially-compromised. As such, the Stromberg patent does not teach treatment of endothelially-compromised VSM with tamoxifen, and does not anticipate present claim 25.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claim 25 under 35 U.S.C. § 102(b).